REMARKS/ARGUMENTS

Claims 2-3, 5-6, 15-16 and 23 are cancelled; no new matter is added.

The obviousness rejection of Claims 1, 4, 7-14, 17-22, and 24-27 based on Sawayanagi, Hidaka, and Dasseux is traversed.

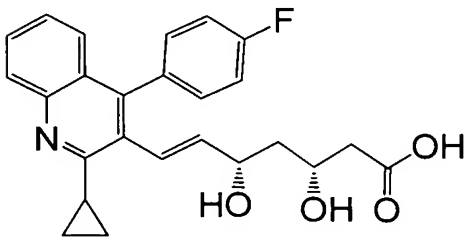
Present Claim 1 is drawn to an external preparation, that is a poultice or plaster, comprising following ingredients (A) and (B): (A) pitavastatin, atorvastatin, a salt of pitavastatin, a salt of atorvastatin, or a combination thereof, and (B) at least one monoterpene selected from the group consisting of menthol, terpineol, citronellal, and combinations thereof, wherein the external preparation does not contain ethanol.

Sawayanagi is drawn to "[a] plaster comprising pranoprofen, a hydrophilic or hydrophobic base component, and an absorbefacient..." (emphasis added, see the Abstract of Sawayanagi). Sawayanagi, at column 2, lines 28-31, describes preferred absorbefacients as being "propylene glycol, diisopropyl adipate, 1-menthol, and benzyl alcohol." Hidaka describes "[a] plaster comprising the film layer which is composed of a film having 0.5 to 4.8 μm thickness....and an adhesive layer (a) which contains a transdermally absorbable drug and is laminated on one surface of said film layer in 2 to 60 μm thickness [that] enables transdermal absorption of a clinically effective amount of a drug with skin rashes reduced" (see the Abstract of Hidaka). The Office, at page 6 of the Official Action, acknowledges "Sawayanagi et al. and Hidaka et al. do not teach the drug [used] in the plaster is pitavastatin, or atrovastatin, or a salt thereof, as claimed...," do not teach "the preparation is a poultice or the preparation contains carmellose sodium and the amounts claimed," and do not teach "the monoterpene used in the plaster preparation is terpineol or citronellal, or the combination thereof, as claimed." The Office therefore relies upon Dasseux to partially remedy the deficiencies of Sawayanagi and Hidaka by providing "croscarmellose sodium" (see page 7 of the Official Action), and further asserts that "because Sawayanagi et al. teach the plaster

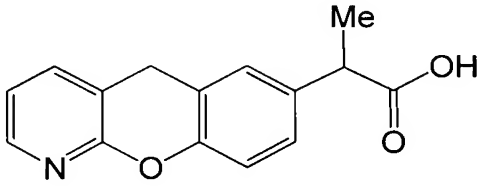
preparation uses menthol as an absorbefacient compound for promoting cutaneous absorption; such teaching would motivate one of ordinary skill in the art to try not only menthol, but also to try other monoterpenes, i.e., terpineol and citronellal..." (see pages 7-8 of the Official Action).

Applicants submit the Office's reasoning is flawed because there is no reasonable expectation of success in combining the references. M.P.E.P. § 2143.02 (I) requires, for making an obviousness rejection, a "reasonable expectation of success." M.P.E.P. § 2143.02 (II) describes, in part, that "[e]vidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness."

At the outset, Applicants note that pranoprofen is a non-steroidal anti-inflammatory and analgesic drug. Pitavastatin, for example, in contrast to pranoprofen, is a statin and an inhibitor of HMG-CoA reductase. The structures of pranoprofen and pitavastatin are shown below:



Pitavastatin



Pranoprofen

A visual comparison of the pitavastatin and pranoprofen reveals that the two compounds, in addition to having different biological functions, and different mechanisms of action, are very different in structure, and therefore have different physical properties as well. Thus, while l-menthol, employed by Sawayanagi as an absorbefacient, may promote cutaneous absorption of pranoprofen, there is no reasonable expectation to think that it would promote cutaneous absorption of a different chemotype (e.g., a statin) that has different biological properties, a

different mechanism of action, a different chemical structure, and different physical properties from pranoprofen.

When pitavastatin, atorvastatin, a salt of pitavastatin, or a salt of atorvastatin, as found in the poultice or plaster of present Claim 1, is used in combination with the menthol, terpineol, citronellal, and combinations thereof of present Claim 1, the menthol, terpineol, citronellal, and combinations thereof improve the percutaneous absorbability of the statin or salt thereof, but many other absorbefacients do not. This is illustrated by the data in Tables 2 and 3, specification pages 22-23, (not of the claimed inventive embodiments) that employ for example, stearic acid (Comparative Example 2), oleic acid (Comparative Example 3), diisopropyl adipate (Comparative Example 4, one of the preferred absorbefacients of Sawayanagi), sorbitan monooleate (Comparative Example 5), urea (Comparative Example 6), and magnesium stearate (Comparative Example 7), as absorbefacients. All of the Comparative Examples 2-7 (not of the claimed inventive embodiments) in Table 2, specification page 22, have low permeability coefficients ranging from 0.7 through 6.1 x 10^{-4} cm/h. In contrast, for example, Examples 2-4 (of the claimed inventive embodiments), Table 1, specification page 21, that employ, respectively, 1-menthol, terpineol, and citronellal as absorbefacients, have high permeability coefficients ranging from 19.3 through 31.4 x 10^{-4} cm/h. Thus, many absorbefacients (e.g., the absorbefacients in Comparative Examples 2-7, not of the claimed inventive embodiments, *supra*) result in low skin permeabilities for statins and salts thereof, whereas only selected absorbefacients, (e.g., the absorbefacients in Examples 2-4, of the claimed inventive embodimetns, *supra*, and in present Claim 1 and the claims depending therefrom) promote high skin permeabilities for statins and salts thereof.

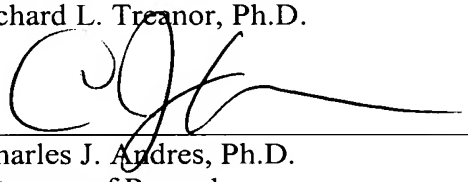
Accordingly, the ability of a substance to improve percutaneous absorbility of a target drug greatly varies depending on the type of substance and the drug, and there is no way to

predict, *a priori*, what effect a particular substance will have on a particular target drug. Absent an ability to predict what effect a particular substance will have on a particular target drug, there is no reasonable expectation of success in combining the references, as required by M.P.E.P. § 2143.02 (I) . Withdrawal of the obviousness rejection is requested.

Applicants submit the present application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Richard L. Treanor, Ph.D.



Charles J. Andres, Ph.D.
Attorney of Record
Registration No. 57,537

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/07)